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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,046	02/04/2000	Sabine Neirynck	VIB-08	8244

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EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,046	NEIRYNCK ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-32,34,36-57* is/are pending in the application.

4a) Of the above claim(s) *42-45 and 47-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-32,34,36-41,46 and 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10/27/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In the paper received October 27, 2003, applicant amended claims 26-32, 34 and 36-57 are pending. Claims 1-25, 33, 35 are cancelled and claims 42-45, 47-51 are withdrawn from consideration due to non-elected subject matter. Claims 26-32, 34, 36-41, 46, and 52-57 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-32, 34, 36-41, 46, and 52-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record.

Applicant asserts that the negative control used by Heinen was not a proper control for administration of a protein vaccine because the administration of the plasmid was administered differently and could have altered the pigs' immune system.

Applicant's arguments and as well as a review of Heinen have been fully considered, but are found unpersuasive. Heinen examined two different immune responses after administering the protein constructs and the DNA plasmids: antibody titers and mean lymphoproliferative responses of PBMCs. The control DNA clearly does not generate any significant immune responses in either category on its own. This lack of immune response is indicative that the

control DNA bears no structural or functional resemblance to the constructs containing M2e administered as vaccines. A negative control is a substance that is known not to contain the ingredient under analysis. The empty plasmid of Heinen does not contain any form of M2e administered and does not generate an immune response. Therefore, the empty plasmid is a proper negative control.

With regard to the difference between modes of delivery, administration of the plasmid encoding M2e induced antibody and PBMC proliferative responses not induced with the negative control. Therefore, it is clearly evident that the empty plasmid negative control, pVR1012, does not induce any immune response compared with the plasmid encoding an M2eNP fusion protein or the M2eHBc fusion protein formulations. Therefore, it is maintained that the empty plasmid of Heinen is a proper negative control.

Applicant states that even if the negative control were proper, Heinen does not show exacerbation of disease upon administration with M2eHBc. Applicant has supplied a teaching from Monto and asserts that fever is a particularly significant marker of severity and treatment progression. Applicant appears to have quoted Monto's conclusion, but the examiner is unable to find the exact excerpt quoted within the abstract. Applicant points to the data in figure 2B of Heinen and states that the pigs that received the negative control had statistically higher temperatures than groups that received M2eHBc fusion proteins. Applicant concludes that antibodies induced by M2eHBc provided protection.

Applicant's arguments, as well as a review of Monto have been fully considered, but are found unpersuasive. The data in figure 2B of Heinen indicates fever in all pig groups. While the negative control group developed the highest fevers on most days, the fevers the experimental

groups developed closely shadow the negative control group and are not significantly different. Since Monto teaches that fever is a clear indicator of influenza and all of the pigs in all of the groups developed fever, it is evident that all vaccine formulations were ineffective.

With respect to the clinical signs, applicant summarizes the teachings of Monto, indicating that only coughing and/or fever are considered reliable indicators of influenza virus infection. Applicant states that the second indicator, coughing, is highly subjective for evaluation and may not be accurately measured by Heinen.

Applicant's arguments have been fully considered, but are found unpersuasive. The evaluation of coughing is not subjective. The subject either coughs or not. In the first paragraph under the "Results" section on page 1854, Heinen assigns "a score of 0 if absent and 1 if present." Further, Monto clearly teaches that the presence of a cough is one of the best clinical signs for determining whether a subject has influenza infection. The pigs evaluated by Heinen clearly had a cough. This symptom, combined with the presence of a fever, is a clear indication of influenza virus infection, according to the teachings of Monto.

Applicant concludes that M2eHBc did not exacerbate flu symptoms in pigs because Heinen indicates that there is no significant difference between the experimental groups and the control group.

Applicant is correct that there was no significant difference between the viral excretion between the different groups. The group that received the negative control, i.e., no protective antigen, had as much viral excretion as the groups that were supposed to have received an efficacious antigen. The fact that there was a comparable amount of virus excreted from the all of the groups is clearly indicative that the pigs were not protected.

Applicant states that Heinen's M2eHBc, human fusion protein would not have been expected to provide heterologous protection against swine influenza virus protection due to the amount of sequence divergence in the M2e protein. Applicant points out that the M2e protein is highly conserved within a single animal species.

Applicant's arguments have been fully considered. It is conceded that the difference in between swine and human influenza virus M2e protein sequences may have contributed to the lack of protective efficacy of M2eHBc fusion proteins administered by Heinen. However, it is noted that the M2e sequence within the DNA construct encoding M2eNP is derived from swine influenza virus strains. This construct was also found to exacerbate disease in pigs. Therefore, the difference between the human and influenza virus M2e sequences as a contributing factor for the lack of protection is only speculative.

Applicant also questions what fraction of the anti-M2e antibodies bound to the swine M2e is represented by Heinen.

Applicant's concerns have been considered. However, the data provided by Heinen is the only data available. The data indicate that anti-M2e antibodies bind to swine M2e. The other data indicate that the construct does not protect against influenza virus challenge.

With regard to mice and pigs as animal models to evaluate influenza virus vaccines, applicant asserts that mice are valid animal models.

In response, it is evident that pigs are also valid animal models for studying influenza vaccines because they are a natural host of influenza virus infection, develop a similar course of disease manifestation upon infection and the same influenza virus strains can infect both pigs and humans. In addition, pigs have been implicated as mixing reservoirs of new influenza virus

strains. See the discussion section bridging pages 1857-1858 of Heinen. The fact that the M2e fusion construct elicits contrasting immune reactions in two different animal models provides sufficient doubt that the construct is predictably efficacious in preventing influenza virus infection. The data of Heinen et al. clearly indicate that the instant fusion protein exacerbates disease in a natural swine host, see the previous citations. Therefore, it is maintained that the skilled artisan would predict that the M2e fusion protein would exacerbate disease in other natural hosts.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley

JAMES HOUSEL 1/12/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600